Development of Tracleer® (bosentan)

- Discovery of ET-1
- First public. on bosentan
- First evidence of efficacy of bosentan in PAH
- 351 study Launch US
- Launch Canada
- BREATHE-1 study
- Launch EU
- Launch Australia
- Launch Japan
- Launch China EARLY
- Creation of Actelion

18 years’ research in ET and ET receptor antagonists, more than 130 manuscripts published by our group
Bosentan (Tracleer®)
Oral dual ET receptor antagonist

Main pharmacological properties of bosentan

- Vasodilation
- Anti-hypertrophic
- Anti-fibrotic
- Anti-inflammatory

Bosentan induces vasodilation

\[ \text{Ach (-log M)} \]

-20  -15  -10  -5  0  5  6  6.5  7  7.5

\[ \text{% Maximum relaxation (Emax)} \]

-20  -15  -10  -5  0  5

\* p < 0.05

In vitro model: Human saphenous veins pre-contracted with phenylephrine

Dumont et al. J Neurosurg. 2001;94:281
Bosentan prevents and reverses vascular hypertrophy

Significant reduction in pulmonary arterial wall thickness vs. control (p < 0.01)

6 wks hypoxia + 4 wks placebo

6 wks hypoxia + 4 wks bosentan

Rat hypoxic model of pulmonary hypertension

Bosentan attenuates pulmonary fibrosis

Control  
Bleomycin  
Bleomycin + Bosentan

Rat model of bleomycin-induced fibrosis

Park et al. Am J Respir Crit Care Med 1997;156:600
Bosentan reduces inflammation

Sephadex (Control)  Sephadex + Bosentan

Rat model of sephadex-induced peribronchial inflammation

Finsnes et al. Am J Respir Crit Care Med 1997;155:1404
Bosentan was tested and showed efficacy in animals models of:

- Hypertension
- Acute renal failure
- Chronic renal failure
- Pulmonary hypertension
- Heart Failure
- Subarachnoid hemorrhage
- Migraine
- Cancer
- Stroke
- Septic shock
- Gastric ulcer
- Inflammatory Bowel Disease
- Diabetes
- Organ transplant
- Cirrhosis
- Pulmonary fibrosis
Bosentan pharmacokinetics

Absorption and distribution

• Orally active
  • Bioavailability 50%, no food effect
• Highly protein bound (98%)

Elimination (half life 5.4 hours)

• Hepatic metabolism
  • Cytochrome P450 (CYP) 3A4 and CYP2C9
    3 metabolites – 1 pharmacologically active
• Biliary excretion
  • < 6% in urine (parent + metabolites)

Bosentan pharmacokinetics

PK parameters following bosentan 125 mg

$C_{\text{max}}$ 1.3 µg/mL (1.1-1.6)
$t_{\text{max}}$ 3.5h (1.7-8.0)
$t_{1/2}$ 5.4 h (4.5-6.4)
$AUC_{0-\infty}$ 8.0 µg • h/mL (6.3-10.0)

(n=16 healthy volunteers)

Bosentan PK is unaffected by food

Bosentan dosing in special populations

Elderly (>65 y): No dose adjustment needed

Renal impairment: No dose adjustment needed
(also with dialysis)

Hepatic impairment:
Mild: No dose adjustment needed
Moderate / Severe: Contra-indicated
No dose adjustment in mild hepatic impairment

## Bosentan exposure in children with PAH

Multiple dose comparison

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>AUC$_\tau$ (ng•h/ml)</th>
<th>C$_{max}$ (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric patients:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 - 20 kg (n=7)</td>
<td>31.25</td>
<td>3496</td>
</tr>
<tr>
<td>20 - 40 kg (n=6)</td>
<td>62.5</td>
<td>5428</td>
</tr>
<tr>
<td>&gt; 40 kg (n=6)</td>
<td>125</td>
<td>6124</td>
</tr>
<tr>
<td>Adult patients</td>
<td>125</td>
<td>8149</td>
</tr>
</tbody>
</table>

Phase exploratoire

Bosentan a été testé chez l’homme dans les indications suivantes:

- Migraine
- Hypertension arterielle
- Insuffisance cardiaque
- Complications des anti-inflammatoires
- Hemorrhagie sous arachnoidienne
- Hypertension pulmonaire
- Angioplasties coronariennes
ENABLE-1 / -2: Study design

NYHA Class IIIB-IV

Placebo BID

62.5 Bosentan 125 BID

4 wk 39 Weeks 600 events

Mean follow-up = 1.5 years

Actelion: Data on file
ENABLE: Death or CHF hospitalization

Pts at risk

Bosentan Placebo

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Pts at risk</th>
<th>Event-free</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>804</td>
<td>807</td>
</tr>
<tr>
<td>26</td>
<td>615</td>
<td>655</td>
</tr>
<tr>
<td>52</td>
<td>542</td>
<td>577</td>
</tr>
<tr>
<td>78</td>
<td>393</td>
<td>388</td>
</tr>
<tr>
<td>104</td>
<td>123</td>
<td>113</td>
</tr>
<tr>
<td>130</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Logrank p-value: 0.8986

Bosentan = 312 events
Placebo = 321 events

Actelion: Data on file
Bosentan, a dual endothelin receptor antagonist improves exercise capacity and hemodynamics in patients with pulmonary arterial hypertension

R. Channick, L. Rubin, G. Simonneau, I. Robbins, V. Tapson, A. Frost, D. Badesch, F. Bodin, S. Roux
<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>D. Badesch</td>
<td>University of Colorado, Denver</td>
</tr>
<tr>
<td>R. Channick</td>
<td>University of California, San Diego</td>
</tr>
<tr>
<td>A. Frost</td>
<td>Baylor College of Medicine, Houston</td>
</tr>
<tr>
<td>I. Robbins</td>
<td>Vanderbilt University, Nashville</td>
</tr>
<tr>
<td>L. Rubin</td>
<td>University of California, San Diego</td>
</tr>
<tr>
<td>G. Simonneau</td>
<td>Hôpital Antoine Beclere, Paris</td>
</tr>
<tr>
<td>V. Tapson</td>
<td>Duke University, Durham</td>
</tr>
</tbody>
</table>
Study design

Bosentan:Placebo = 2:1

Period 1 (fixed duration)
- Weeks 0-12
  - Baseline
  - Placebo: 62.5 mg bid
  - Bosentan: 125 mg bid

End-point

Period 2 (variable duration)
- Weeks 12-28

Channick et al. Lancet 2001;358:1119
6-Minute walk test
Change from baseline over time

Placebo (n = 11)
Bosentan (n = 21)

Channick et al. Lancet 2001;358:1119
WHO functional class
Change from baseline to week 12

Baseline

Week 12

Placebo (n = 11)
Bosentan (n = 21)

Channick et al. Lancet 2001;358:1119
Hemodynamics
Change from baseline to week 12

Cardiac index
Mean pulmonary arterial pressure
Pulmonary vascular resistance

Week 12
Week 12
Week 12

Placebo (n = 10)
Bosentan (n = 20)

Channick et al. Lancet 2001;358:1119
Clinical worsening within 28 weeks

- Placebo (n = 11)
- Bosentan (n = 21)

\[ P = 0.03 \]

Channick et al. Lancet 2001;358:1119
TRACLEER™ (bosentan)

BREATHE-1
BREATHE-1
Bosentan randomized trial of endothelin receptor antagonist therapy for pulmonary hypertension:

- 11 countries, 27 sites, 213 patients
- Mid-July 2000 to Dec 2000
- Last patient last visit: March 30, 2001
Objectives of BREATHE-1

- To confirm the positive effects of bosentan on exercise capacity in PAH
- To evaluate the effect of bosentan on time to clinical worsening (16 and 24 weeks)
- To explore the dose response of two doses of bosentan on exercise capacity
- To evaluate the safety and tolerability of bosentan

Rubin et al. NEJM 2002;346:896
Study design

**Screening**

- **Placebo**
- **Bosentan 62.5 mg bid**

**Period 1 – Evaluation Period**

- **Placebo**
- **Bosentan 62.5 mg bid**
- **Bosentan 125 mg bid**

**Period 2 (first 48 patients)**

- **Bosentan 250 mg bid**

**End-point: Week 16**

Rubin et al. NEJM 2002;346:896
Definition of time to clinical worsening

Shortest time to either:

• Death
• Premature withdrawal
• Hospitalization due to PAH worsening
• Initiation of prostacyclin therapy

Rubin et al. NEJM 2002;346:896
Walk test ITT
Change from baseline to week 16

Placebo (n = 69)  Bosentan (n = 144)

Δ Walk distance (meters)

Baseline  Week 4  Week 8  Week 16

62.5 mg/bid  125 or 250 mg/bid

p = 0.0002  Mean ± SEM

Rubin et al. NEJM 2002;346:896
Borg dyspnea index
Change from baseline to week 16

$p = 0.0587$

Rubin et al. NEJM 2002;346:896
Time to clinical worsening
Up to 16 weeks

Event-free (%)

Time (weeks)

Rubin et al. NEJM 2002;346:896
Time to clinical worsening
Up to 28 weeks

Rubin et al. NEJM 2002;346:896
Dose response

Exploratory analysis
Walk test ITT
Change from baseline to week 16

- Bosentan 125 mg (n = 74)
- Bosentan 250 mg (n = 70)
- Placebo (n = 69)

Δ Walk distance (meters)

Mean ± SEM

Rubin et al. NEJM 2002;346:896
Time to clinical worsening
Up to 28 weeks

Rubin et al. NEJM 2002;346:896
BREATHE-1 maintenance of efficacy
Walk test up to 28 weeks

Frost et al. JACC 2004 (supplement) - abstract
BREATHE-1 echocardiographic substudy: RV diastolic remodeling index
Change from baseline to week 16

Remodeling index = Min/Max

Treatment effect = -0.06, \( p = 0.012 \)

Galiè et al. JACC 2003;41:1380
### Liver function tests

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 69)</th>
<th>Bos. 125 mg (n = 74)</th>
<th>Bos. 250 mg (n = 70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic function abnormal</td>
<td>2 (3%)</td>
<td>3 (4%)</td>
<td>10 (14%)</td>
</tr>
<tr>
<td>(investigator-reported)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3X ULN</td>
<td>0 (0%)</td>
<td>10 (14%)</td>
<td>10 (14%)</td>
</tr>
<tr>
<td>8X ULN</td>
<td>0 (0%)</td>
<td>2 (2.7%)</td>
<td>5 (7.1%)</td>
</tr>
<tr>
<td>Transient cases</td>
<td>- -</td>
<td>7 (10%)</td>
<td>3 (4.3%)</td>
</tr>
<tr>
<td>Permanent discontin.</td>
<td>- -</td>
<td>0 (0%)</td>
<td>3 (4.3%)</td>
</tr>
</tbody>
</table>

Actelion: Data on file
BREATHE-1 Conclusion

Bosentan (Tracleer®) is a dual endothelin receptor antagonist which is an effective oral treatment for patients with PAH

Rubin et al. NEJM 2002;346:896
Galiè et al. JACC 2003;41:1380
Observed and predicted survival
Kaplan-Meier survival estimates with 99% CI

169 Patients at risk
167 163 153 113 23 16

Event Rate / year (exponential): 5.5%

Observed 1
Predicted (NIH 2)

1 Mc Laughlin et al, Eur Resp J 2005; 25:244-249
Evolution of Eisenmenger syndrome (1)

ASD, VSD or complex defect increases pulmonary blood flow via left-to-right shunt.
Over time, pulmonary resistance rises and results in bi-directional flow.
Evolution of Eisenmenger syndrome (3)

Pulmonary artery pressure rises further with reversal of shunt: right-to-left → Eisenmenger syndrome – patient becomes cyanotic
BREATHE-5: Bosentan improves hemodynamics and exercise capacity in the first randomized placebo-controlled trial in Eisenmenger physiology

Nazzareno Galiè, Maurice Beghetti, Michael Gatzoulis, John Granton, Rolf Berger, Andrea Lauer, Eleonora Chiossi, Michael Landzberg on behalf of the BREATHE-5 Investigators

Rationale

- ET-1 implicated in Eisenmenger syndrome (1-3)
- Bosentan, a dual ERA, has been shown to be effective in treating PAH
- Small open-label bosentan studies have shown benefits in ES patients (4-7)
- Placebo-controlled study needed to clarify safety and efficacy (8)

(2) Humbert M, J Am Coll Cardiol 2004: S13-S24
(3) Cacoub P, Am J Cardiol 1993; 71(5):448-450
(4) Christensen DD, Am J Cardiol 2004; 94(2):261-263
(7) Schulze-Neick I, Am Heart J 2005; 150(4):716
(8) Galiè N et al, Circulation 2006; 114:48-54
Objectives of the study

To evaluate in a randomized controlled trial in patients with Eisenmenger syndrome the effects of bosentan on:

- Overall shunting (SpO2)
- Cardiopulmonary hemodynamics (PVRi)
- Exercise capacity (6MWD)

Study design

Screening

2:1 Randomization

Baseline

2 weeks

4 weeks

12 weeks

16 Weeks

Bosentan 62.5 mg bid

Bosentan 125 mg bid

Placebo 62.5 mg bid

Placebo 125 mg bid

## Bosentan does not reduce Sp0₂

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=17)</th>
<th>Bosentan (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SE)</td>
<td>Mean (SE)</td>
</tr>
<tr>
<td>Baseline (%)</td>
<td>83.6 (1.2)</td>
<td>82.4 (0.9)</td>
</tr>
<tr>
<td>Week 16 (%)</td>
<td>84.0 (1.6)</td>
<td>83.8 (0.9)</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>0.4 (0.9)</td>
<td>1.5 (0.4)</td>
</tr>
</tbody>
</table>

Treatment effect: + 1.0 (0.9)

95 % CI =[-0.7 , 2.8] > -5, non-inferiority shown

Bosentan reduces pulmonary vascular resistance indexed

Placebo (n=17) Bosentan (n=36)

T.E. = -472 dyn.sec.cm⁻⁵
p=0.04

T.E. = -472 dyn.sec.cm⁻⁵
p=0.04

Bosentan increases exercise capacity

WHO functional class

Placebo (n = 16)

Bosentan (n = 37)